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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
GAMBEL, PHILLIP	

ART UNIT	PAPER NUMBER
1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/754004	Applicant(s) FELDMAN
	Examiner GIMIE	Art Unit 1644

– The MAILING DATE of this communication appears on the cover sheet with the correspondence address –

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☑ Responsive to communication(s) filed on 8/25/03

2a)☑ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☑ Claim(s) _____ is/are pending in the application. 1-23, 29-38

4a) Of the above claim(s) _____ is/are withdrawn from consideration. 7-10, 20-23, 29-38

5)☐ Claim(s) _____ is/are allowed.

6)☑ Claim(s) _____ is/are rejected. 1-6, 11-19

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☑ The translation of the foreign language provisional application has been received.

15)☑ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☑ Notice of References Cited (PTO-892) REFERENCE NOT PROVIDED CITED BY APPLICANT

2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3)☑ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.

4)☐ Interview Summary (PTO-413) Paper No(s). _____.

5)☐ Notice of Informal Patent Application (PTO-152)

6)☐ Other:

PAPER NO. 16

DETAILED ACTION

1. Applicant's amendment, filed 8/25/02, has been entered.
Claims 24-28 have been canceled.
Claims 1 and 4 have been amended.

Claims 1-6 and 11-19 as they read on methods of treating TNF-mediated diseases as it reads on psoriasis and psoriatic arthritis with methotrexate and TNF-specific antibodies are under consideration in the instant application.

Claims 7-10, 20-23 and 29-38 have been withdrawn from consideration by the examiner 37 CFR 1.142(b), as being drawn to a nonelected invention and/or species (e.g. rheumatoid arthritis and Crohn's disease).

2. The text of those sections of Title 35 USC not included in this Action can be found in a prior Action.
This Action will be in response to applicant's arguments, filed 8/25/03.
The rejections of record can be found in previous Office Action, mailed 12/9/02.

3. It is noted that applicant's amendment, filed 8/25/03, maintains priority back to USSN 07/958,248, filed 10/8/92, but did not address the following priority issues of record.

Again, applicant is invited to indicate the priority of the instant claims.

As pointed out previously, the filing date of the instant claims is deemed to be the filing date of parent application USSN 08/690,775, i.e. 8/1/96. Previously, it was pointed out that priority application USSN 08/403785 and PCT/GB94/00462 does not support the broader claims of the instant application, including "preventing a tumor necrosis factor-mediated disease", "tumor factor-mediated disease", "binds to one or more amino acids of hTNFα selected from the group consisting of about 87-108 and about 58-80", "cA2" and "epitope of cA2" .

It is noted that applicant has amended claims 1 and 4.

If applicant desires priority prior to 8/1/96; applicant is invited to point out and provide documentary support for the priority of the instant claims. Applicant is reminded that such priority for the instant limitations requires written description and enablement under 35 U.S.C. § 112, first paragraph.

4. Formal drawings have been submitted which comply with 37 CFR 1.84.

5. Applicant's amended claims, filed 8/25/03 has obviated the previous rejection under 35 U.S.C. § 112, second paragraph, with respect to the recitation of "tumor necrosis factor-mediated disease"

6. Claim 1-6, 11, 13, 14 and 19 stand rejected under 35 U.S.C. § 102(e) as being anticipated by Mak et al. (U.S. Patent No. 6,190,691) (1449; #AK) (see entire document) essentially for the reasons of record.

Applicant's arguments, filed 8/25/03, have been fully considered but are not found convincing essentially for the reasons of record set forth in the previous Office Action, mailed 12/9/02.

Applicant argues that the teachings of Mak results in a combined total of examples numbering in the hundreds. Applicant further asserts that there is no specific disclosure of the claimed combination of methotrexate and a TNFα antagonist. Applicant asserts that the combination of agents used in the claimed invention represents only one of an astronomical number of permutations of the pharmacological agents disclosed by Mak.

In contrast to applicant's assertions, when the species is clearly named, the species claim is anticipated no matter how many other species are additionally named. See Ex parte A, 17 USPQ2d (Bd. Pat. App. & Inter. 1990) and MPEP 2131.02.

As pointed out previously, Mak et al. teach the use of TNF antagonists, including anti-TNF antibodies and fragments thereof (e.g. column 7, paragraph 3; column 9, paragraph 3; column 11, paragraph 3; column 42, paragraph 3) in combination with methotrexate (column 41, paragraph 2; Immunosuppressants; columns 59-61, including column 60, paragraph 1) in various dosages and schedules encompassed by the claimed methods (columns 53-56) to treat psoriasis and psoriatic rheumatism (see entire document, Summary of the Invention, Detailed Description of the Invention, including columns 59-61, Treatment of Skin Diseases). Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations, including the epitope specificities and dosing schedules would be inherent properties of the referenced methods to treat psoriasis and psoriatic rheumatism with anti-TNF antibodies and methotrexate. Given the inhibitory properties of the referenced anti-TNF antibodies, the claimed functional properties and epitope specificities, including the cA2 competing antibodies would have been inherent properties of the referenced anti-TNF antibodies (e.g. column 7, paragraph 3; column 9, paragraph 3; column 11, paragraph 3; column 42, paragraph 3) .

Applicant's arguments are not found persuasive.

7. Claims 1-6, 11-14 and 16-19 stand rejected under 35 U.S.C. § 103 as being unpatentable over Mak et al. (U.S. Patent No. 6,190,691) AND/OR Adair et al. (U.S. Patent No. 5,994,510) in view of the Merck Manual of Diagnosis and Therapy (Sixteenth Edition, 1992; pages 1338 and 2435-2437) and Aggarwal et al. (U.S. patent No. 5,672,347) (1449, #AF).

Applicant's arguments, filed 8/25/03, have been fully considered but are not found convincing essentially for the reasons of record set forth in the previous Office Action, mailed 12/9/02.

Applicant asserts that a prima facie case of obviousness has not been established.

Applicant's arguments and the examiner's rebuttal concerning Mak is addressed above.

Applicant asserts that the prior art references teach treating the disorder with one of the claimed agents but not combination of the agents in the claimed methods.

In addition, applicant asserts that the results exemplified in the specification support the unexpected results of the claimed combination therapy (e.g. see Figures 1A, 2A, 3A, 4A, 5A; page 3, lines 18-24, Examples 1-3; page 35, lines 5-8, page 37, lines 1-3, pages 36-37, Table 3; pages 38-39, Table 4; page 46, lines 24-47, line 8 of Example 1; page 48, lines 20-50, line 8 of Example 2; and page 51, lines 8-32 of Example 3 of the specification).

In addition, applicant cites Verhoeven et al. ((Br. J. Rheumatol. 37: 612-619, 1998) (Exhibit 1)to underscore the fact that superior effects of a particular combination therapy in the treatment of inflammatory diseases are not predictable absent experimentation.

Applicant's reliance on unexpected results do not overcome clear and convincing evidence of obviousness. Also see Richardson-Vicks Inc. v. Upjohn Co., 44 USPQ2d 1181 (CAFC 1997)

In contrast to applicant's assertions, the prior art provides sufficient motivation and expectation success of combining anti-TNF antibodies and methotrexate in the treatment of inflammatory conditions, including psoriasis and psoriatic rheumatism.

As pointed out previously, the following of record is reiterated for applicant's convenience.

Mak et al. teach the use of TNF antagonists, including anti-TNF antibodies (e.g. column 7, paragraph 3; column 9, paragraph 3; column 11, paragraph 3; column 42, paragraph 3) in combination with methotrexate (column 41, paragraph 2; Immunosuppressants; columns 59-61, including column 60, paragraph 1) in various dosages and schedules (columns 53-56) to treat psoriasis and psoriatic rheumatism (see entire document, Summary of the Invention, Detailed Description of the Invention, including columns 59-61, Treatment of Skin Diseases). Mak et al. differs from the claimed invention by not disclosing the well known use of recombinant antibodies.

Adair et al. teach the use of recombinant anti-TNF antibodies and fragments thereof to treat autoimmune diseases, including psoriasis and arthritis (see column 11, paragraph 8), alone or in combination with other active ingredients (column 11, paragraph 5), including well known methods of modes of administration (column 12)(see entire document). Adair et al. differs from the claimed methods by not disclosing the well known use of methotrexate in the treatment of psoriasis and psoriatic arthritis

Merck Manual of Diagnosis and Therapy (Sixteenth Edition, 1992) disclose the well known use of methotrexate in the treatment of psoriasis and psoriatic arthritis; pages 1338 and 2435-2437).

Given the teachings of Mak et al., Adair et al. and the Merck Manual of Diagnosis and Therapy, one of ordinary skill in the art at the time the invention was made would have been motivated to select the combination of anti-TNF antibodies in combination with the immunosuppressant methotrexate to treat psoriasis and psoriatic rheumatism (e.g. psoriatic arthritis). Given the inhibitory properties of the referenced anti-TNF antibodies by Mak et al. and Adair et al., the claimed functional and epitope specificities, including the cA2 competing antibodies would have been expected or intrinsic properties of the referenced anti-TNF antibodies. Providing the claimed recombinant anti-TNF antibodies and fragments thereof encompassed by the instant claims (e.g. chimeric, humanized, resurfaced antibody) would have been obvious to the ordinary artisan to provide therapeutic antibodies in order to decrease the immunogenicity of therapeutic antibodies and to increase half-life of antibodies to achieve effective amounts of anti-TNF antibodies. Rheumatism refers to a variety of disorders marked by inflammation, degeneration or metabolic derangement of the connective tissue structures, including The joints and when it is confined to joints it refers to arthritis. The Merck Manual notes that psoriasis is associated with joint involvement known as psoriatic arthritis. The various therapeutic modalities are either explicitly taught by Mak et al. or would have been obvious to one of ordinary skill in the art to provide effective therapeutic amounts of immunosuppressive regimens in order to meet the needs of the patients, herein, patients with psoriasis and psoriatic arthritis.

In addition to teaching the use of anti-TNF antibodies to treat various autoimmune diseases, Aggarwal et al. teach that the combination of TNF antagonists and anti-inflammatory agents provides for the use of these agents in lesser dosages when used alone. An ordinary artisan would have been motivated to provide anti-TNF antibodies to lessen the amount of methotrexate, given its know toxicities at the time the invention was made. It was prima facie obvious to combine two compositions each of which is taught by prior art to be useful for same purpose in order to form third composition that is to be used for very same purpose; idea of combining them flows logically from their having been individually taught in prior art. See MPEP 2144.06. Here, the prior art teaches combining antagonists encompassed by the claimed invention by teaching the use of anti-TNF antibodies and/or methotrexate to treat psoriasis and psoriatic arthritis with other agents to inhibit the same disease. Here, too, the references teach the art known advantages of employing two immunosuppressives at the time same time, as evidenced by Aggarwal. et al.

While applicant assertions of unexpected results in combination with Verhoeven et al. ((Br. J. Rheumatol. 37: 612-619, 1998) (Exhibit 1) are acknowledged, the prior art clearly provide the rationale for combining anti-TNF antibodies in combination with methotrexate in a recognition in the art that there were advantages or beneficial results produced by their combination. Therefore, in this instance, there was sufficient motivation and expectation of success in combining anti-TNF antibodies and methotrexate in the treatment of psoriasis and psoriatic arthritis at the time the invention was made.

From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention

Applicant's arguments are not found persuasive.

8. Claims 14-15 stand rejected under 35 U.S.C. § 103 as being unpatentable over Mak et al. (U.S. Patent No. 6,190,691)(1449; AK) AND/OR Adair et al. (U.S. Patent No. 5,994,510) in view of the Merck Manual of Diagnosis and Therapy (Sixteenth Edition, 1992; pages 1338 and 2435-2437)and Aggarwal et al. (U.S. patent No. 5,672,347) (1449, #AF),
as applied to claims 1-6, 11-14 and 16-19 above and further in view of Le et al. (U.S. Patent No. 5,919,452) (1449; # AD) for the reasons of record set forth in the previous Office Action, mailed 12/9/02.

Applicant's arguments, filed 8/25/03, have been fully considered but are not found convincing essentially for the reasons of record set forth in the previous Office Action, mailed 12/9/02.

Applicant's arguments and the examiner's rebuttal are essentially the same as addressed above. Applicant's arguments are not found persuasive.

9. Claims 1-6 and 11-19 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-30 of U.S. Patent No. 6,270,766. Although the conflicting claims are not identical, they are not patentably distinct from each other because the patented claims anticipate the instant claimed methods.

In the absence of a rebuttal in applicant's amendment, filed 8/25/03, it appears that applicant has acquiesced to the double patenting rejection of record.

10. Claims 1-6 and 11-19 stand are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 32-37, 42-50, 55-64 (or appropriate pending claims) of copending application Serial No. 09/921,937. This is a *provisional* double patenting rejection since the conflicting claims have not in fact been patented.

In the absence of a rebuttal in applicant's amendment, filed 8/25/03, it appears that applicant has acquiesced to the double patenting rejection of record.

11. No claim is allowed.

12. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (703) 308-3997. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. a message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 872-9306

Phillip Gambel, Ph.D.
Primary Examiner
Technology Center 1600
November 3, 2003